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STEM CELLS AND SOCIETY

Sarah Theresa Clancey
Worcester Polytechnic Institute

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STEM CELLS AND SOCIETY

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Sarah Clancey

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APPROVED:

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Prof. David S. Adams, Ph.D.
WPI Project Advisor

ABSTRACT

"Stem Cells and Society" aims to delve into the controversial nature of the stem cell debate and provide the background necessary to form an educated opinion on the topic. These undifferentiated cells come from many sources and have great potential for therapeutic use. The first two chapters provide the necessary scientific information to understand the basics of the topic, while the last two chapters explore the ethics of stem cell use, particularly embryonic stem cell use, and the politics and legislation pertaining to the use of stem cell research and its funding in the US and internationally. The research performed for this project has allowed for the author's personal conclusions which shall also be discussed. This research has the ability to make a huge impact on our society.

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PROJECT OBJECTIVES

This IQP was undertaken with the objective to provide unbiased information with regard to the stem cell controversy. This technology has the ability to impact our society and provide advances in healthcare; however, the means to which those advances are obtained is a topic of strong debate. Chapter-1 explains the many different types of stem cells and their sources, and the purpose of Chapter-2 is to provide examples of applications of these various stem cells as an introduction for discussing stem cell benefits to society. The applications discussed in this project included past and current research, clinical trials, and potential future experiments. The object of Chapter-3 is to expose the ethical concerns pertaining to stem cell research, and to discuss the variety of positions taken by the main world religions. Chapter-4 investigates the changes in policies regarding stem cell and embryo research in the Unites States and internationally. The project will conclude with opinions the author has formed as a result of the research performed for the project, as well as an example of which government's legislation best fits the author's main views.

Chapter-1: Stem Cell Types and Sources

Stem cells are long lived cells with the ability to differentiate into other cell types. Due to this tissue-forming potential, stem cells are the center of the medicine of the 21st century, regenerative medicine. However, stem cell research has become the center of much controversy, both medically and politically. A common misconception is that stem cells are all alike, and more importantly that all stem cells destroy embryos in order to obtain them. Therefore, it is very important to understand the different types of stem cells, where they come from, how they can be used, and which are of greatest ethical concerns. The purpose of this chapter is to describe the various stem cell types and where they are obtained.

Stem Cell Classifications

Stem cells can be classified by their abilities to form different types of cells. The more tissues that can be formed from a stem cell, the higher its *potency*. *Totipotent* cells have the ability to form both the placenta and the entire rest of the organism. Only the zygote and cells through the 8-cell stage are totipotent. Embryonic stem (ES) cells (obtained from embryos) are characterized as *pluripotent* stem cells. They do not have the ability to create the placenta, but they have the ability to form any other type of cell in the body. ES cells can divide in culture and have much therapeutic potential, but are also at the heart of the stem cell controversy. The least controversial are the adult stem cells (ASCs) which are isolated from adult tissues. ASCs are *multi-potent* and have a more limited ability to differentiate into a few related cell types. For example, cardiac stem cells have the ability to form myocytes, smooth and endothelial vascular

cells (Beltrami et al., 2003), but not neural or bone cells. Other types of ASCs are classified as unipotent; they have the ability to create only one type of cell. The ability to differentiate into many different tissues makes both pluripotent and multi-potent stem cells very useful medically, and the center of many research laboratories around the world.

Embryonic Stem Cells

What sets embryonic stem cells apart from any other type of stem cell, and why are they so valuable? The most important property of the ES cell is its pluripotent ability to form any cell of the three embryonic germ layers (mesoderm, ectoderm, and endoderm). If we can produce any cell type *in vitro*, drugs can be safely tested on human cells in culture before testing the drug in humans. This would provide a more accurate determination of both the medicine's capability to treat the illness and the safety of the substance. The tissue forming capacity of ES cells can also be used to form healthy tissue that can be transplanted into patients afflicted with degenerative diseases, and the study of these cells can deepen our knowledge of early embryonic development (Thomson and Yu, 2006). These are just a few of the benefits of using ES cells. However, this is a controversial issue and the method of producing ES cell lines destroys embryos.

The embryos used to provide ES cells are formed by *in vitro* fertilization (IVF) at IVF clinics. The clinics sometimes end up with unused frozen embryos, and rather than dispose of them, these extra embryos can sometimes be used for research (with the proper consent). The fertilized embryos are grown *in vitro* about 5 days to the blastocyst stage, where the embryo consists of a hollow ball of cells. The inner cell mass (ICM) of the blastula are ES cells. (Thomson and Yu, 2006). The ES cells are isolated and grown into ES cell lines (**Figure-1**).

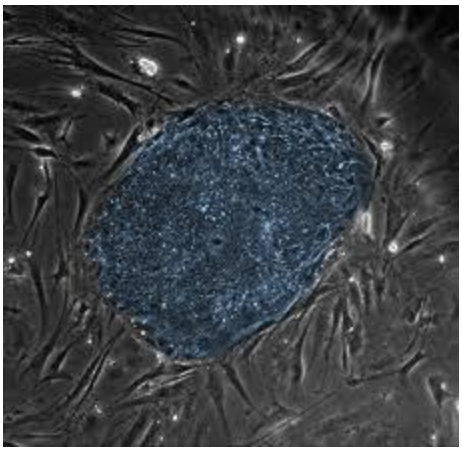

Figure 1: Photograph of Embryonic Stem Cell Line. The blue cells are a colony of ES cells. (Yamanaka, 2011)

In order for an ES cell line to be accepted as truly pluripotent, it is crucial that the cells proliferate, remain undifferentiated in culture, and be capable of forming all three embryonic germ layers. In order for cells to have an indefinite life span, the expression of telomerase enzyme (that helps maintain chromosome structure) must be significantly greater than the level found in a normal somatic cell. Telomerase adds telomere caps to the end of DNA in order to keep the important DNA sequences from being lost after every cell division. Also ES cells contain specific cell surface markers which vary depending on the species. For example, SSEA-1(stage specific embryonic antigen) is highly expressed in mouse ES cells, while in human ES cells the levels of SSEA-3 and SSEA-4 are highly expressed (Appendix C, 2009). Other human ES cell surface markers include antigens TRA-1-60 and TRA-1-81, as well as alkaline phosphatase. The ES cells are stained with antibodies to determine whether these specific markers are present (Thomson and Yu, 1998).

The creation of an ES cell line was first accomplished using mouse cells in 1981 by two different groups, one led by Gail Martin (Martin, 1981) and the other led by Evans and Kaufman (1981). These groups produced ES cells in culture that displayed all of the proper characteristics of pluripotent cells and the cell surface marker SSEA-1 that is highly expressed by undifferentiated mouse cells. During this experiment, the use of a control culture showed the researchers that a conditioned medium was necessary for the cultured ES cells to proliferate indefinitely and remain undifferentiated (Martin, 1981). Since their original experiments, optimal culture media have been found for growing mouse ES cells.

After over ten years of work with mouse and primate ES cells, in 1998 the first human ES cell line was produced (Thompson et al., 1998; Shamblott et al., 1999). This was accomplished by two different groups. One team led by James Thomson obtained their ES cells from IVF embryos (which became the standard method of isolation), while the other team led by John Gearhart obtained their ES cells from aborted fetuses (Chamany, 2004). Thomson was able to produce five ES cell lines, and they were cultured and tested for the proper characteristics of pluripotent cells. The cells remained undifferentiated, but when stimulated could produce cells from all the three germ layers. The cells also continued to proliferate in an undifferentiated state for a prolonged time. Telomerase levels were significantly higher than the levels found in somatic cells, and the appropriate cell surface markers were present (Thomson et al., 1998).

The destruction of the embryo when the ES cells are isolated is the center of the stem cell ethical debate, so the arguments eventually focus on the rights of the embryo (discussed in Chapter-3). Although ES cell research continues to the extent allowed by Congress, and some ES cell lines have even made it to human clinical trials which will be discussed in Chapter-2, alternative sources for pluripotent cells have been explored due to the controversial nature of using human embryos for research.

Induced Pluripotent Cells

One of the most recent steps forward in stem cell research was the formation of induced pluripotent stem cells (iPS cells), which are normal somatic cells programmed to dedifferentiate into pluripotent cells (**Figure-2**). This amazing feat was first accomplished by Shinya Yamanaka and his research team in 2006 for mice (Takahashi and Yamanaka, 2006). The team achieved this by using retroviruses to insert four different genes into the DNA. The original genes used

were Oct3/4, Sox2, Klf4, and c-Myc, a combination found by combining different sets of the 24 genes known to be highly expressed in mouse ES cells (Vogel, 2006). One year later, the same four factors were used to derive human iPS cells (Takahashi et al., 2007). This was a huge accomplishment, because if iPS can be perfected for clinical use, normal adult somatic cells can be taken from a patient to derive iPS cells genetically identical to the patient, so immune rejection would be minimized.

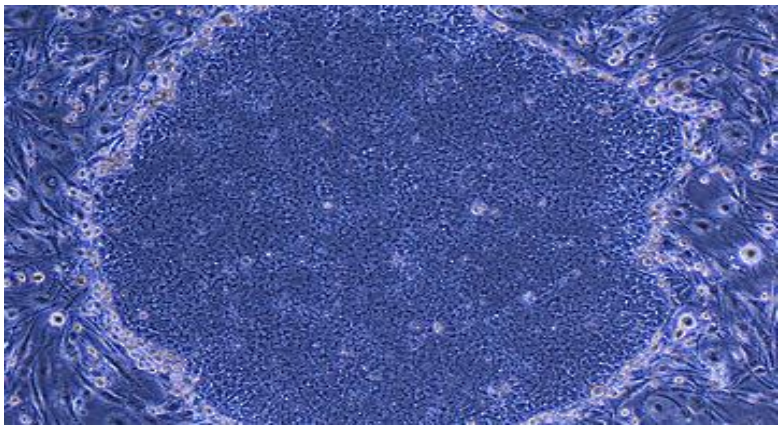

Figure-2: **Induced Pluripotent Stem Cells from Shinya Yamanaka's Laboratory.** (Glennon, 2003)

The current debate is whether iPS cells are truly pluripotent. Initially they appeared to be able to form any type of cell in the body, but more proof was needed, so two research teams led by Qi Zhou and Fanyi Zeng produced live mice from iPS cells. They accomplished this by making a tetraploid embryo and then placed the iPS cells into the embryo. Using this method, they produced live mice, proving that iPS cells had the same developmental ability as ES cells. However, their success rate was very low, hundreds of embryos were created, and less than 5% survived, and many of the mice produced died young (Cyranoski, 2009). More recently, scientists have shown that human iPS cells may grow slower in culture than ES cells, and may

contain genetic mutations (Lister et al., 2011). A research team in Boston found significant differences in gene expression on chromosome twelve when analyzing the DNA of murine ES cells and iPS cells. Many sequences that were activated in ES cells were silenced in the iPS cells, which could account for the inefficiency of iPS cells (Doglin, 2010).

As promising as iPS cells are, many obstacles must be overcome before they are used therapeutically. These cells can be very dangerous because they are prone to causing tumors. Several research teams are looking into the various possible causes of this major drawback. When using viral vectors to carry the desired genes into the cell, their haphazard insertion into chromosomes can cause damage; therefore some scientists are testing a viral-free method of gene delivery (Kaji et al., 2009). Another issue is that two of the four genes typically inserted (c-Myc and Klf4) are oncogenes, so eventually iPS cells were derived omitting those two factors by using only two genes (Kim et al., 2008). It has also been found that the absence of the tumor suppressing protein p53 alleviates some of the difficulties of creating iPS cells, especially when using somatic cells from adults. However, the absence makes the cell unstable and prone to tumors. Therefore, researchers need to find a way to ensure that p53 can be reactivated and remain activated once they have produced the desired iPS cell (Normile, 2009).

Some researchers are focusing on methods to reduce the level of mutations in iPS cells. Using fewer transduced genes helped (Kim et al., 2008). Another method eliminated the viral delivery vector. Although the first successful method used retroviruses, this can cause significant genetic damage due to its random insertion into chromosomes, so researchers then used adenoviruses or transposons to transfer the genes. These methods work, however, there has been a safer, although less efficient, method that decreases the risk of genetic mutation and cancer. Sheng Ding and his team in California delivered the transforming proteins directly into

the cell, rather than the genes, to decrease the level of genetic mutation (Reprogramming, 2009). If this method could be perfected, the therapeutic use of safe iPS cells could become closer to reality.

Parthenogenetic Embryonic Stem Cells

There is so much controversy surrounding the use of ES cells for research that looking for alternatives is crucial. Parthenogenesis is a very appealing alternative. Several insect species naturally reproduce via parthenogenesis, but not mammals (Holden, 2002). To reproduce via parthenogenesis (a type of asexual reproduction), the egg is chemically stimulated, and it starts replicating without sperm. Although mammals do not reproduce this way, eggs can be stimulated *in vitro* to produce parthenote zygotes that sometimes live long enough to make a blastula from which ES cells can be isolated. Because the mammalian parthenote embryo cannot survive long enough to make an adult, some ethicists believe it may be less ethically controversial than working with fertilized embryos (Brevini and Gandolfi, 2007). Since the parthenote cannot develop full term, their manipulation is not as controversial.

Parthenogenesis is able to be induced in mammals by electrically or chemically stimulating the egg. The stimulation increases the intracellular levels of calcium that the egg normally receives during fertilization (Chamany, 2004). This can be achieved by the addition of chemicals such as calcium ionophore which induces the flow of calcium, followed by the application of 6-dimethylaminopurine (6-DMAP) which prevents the egg from stopping replication (Mitalipov, 2001). Once parthenogenesis has been induced, the egg is able to duplicate the maternal chromosomes to maintain a normal complement of chromosomes (**Figure-3**). However, because the embryo will only have the maternal chromosomes, it is not

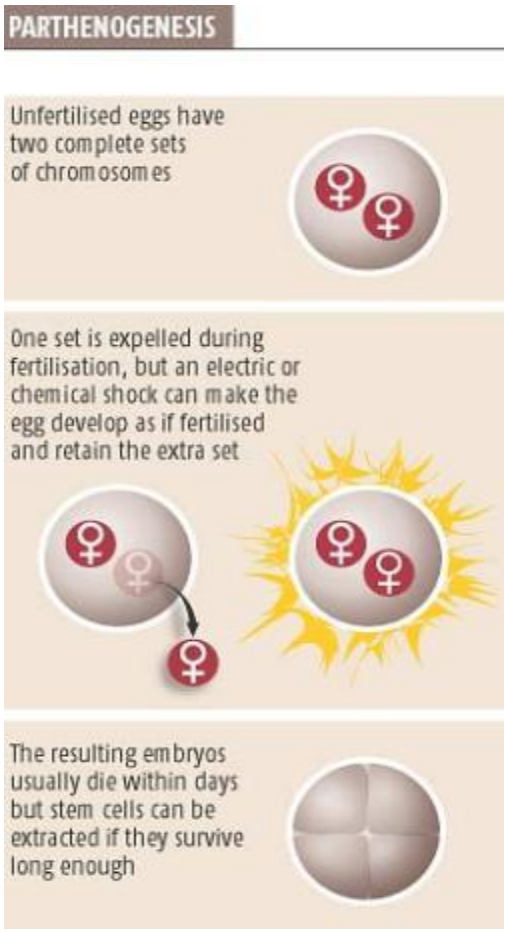

Figure 3: The Steps of Mammalian Parthenogenesis. (www.newscientist, 2011)

able to develop full term, as both maternal and paternal sets of chromosomes are needed for a mammalian embryo to fully develop (Brevini and Gandolfi, 2007). Also, the derived ES cells would match the female egg donor genetically, but not a male.

The first mammalian ES cell line produced by parthenogenesis was from a mouse embryo (Brevini and Gandolfi, 2007). This was accomplished in the early 1980's by Kaufmann and his colleagues who were able to produce murine parthenotes and establish pluripotent stem cell lines from the blastocyst. Primate parthenote ES lines were first established in 2002 in Worcester, MA, at Advanced Cell Technology (Cibelli et al., 2002). This same research group claims success with human parthenotes, but the result remains controversial, the parthenote did not reach the blastocyst stage. However, the approach shows promise for the future of human embryos produced by parthenogenesis and eventually their potential for therapeutic use.

Adult Stem Cells

A wide range of adult stem cells have been discovered. Some have been used to treat people for almost fifty years, and some have only recently been found despite the popular belief of their non-existence. Adult stem cells are mostly multi-potent (but not pluripotent), and

therefore are restricted to the types of cells that they can generate. Adult stem cells are hard to isolate, and do not grow well in culture. However, treatments using adult stem cells are less controversial, and as a result, they are more available for research. Several therapies are already in use in clinical trials, and even more are still being worked on in the laboratory. Recent findings suggest that adult stem cells have a greater plasticity than originally thought; however, it has yet to be proved that their "plasticity" is the product of true trans-differentiation and not simply the result of cell fusion, so we use the term loosely.

Hematopoietic Stem Cells

Hematopoietic stem cells (HSCs) are the best characterized type of stem cell, and have already been in use therapeutically for over 40 years. HSCs actively replenish the supply of blood cells within the body; they primarily reside in the bone marrow and some are located in the peripheral blood. HSCs are difficult to identify, they look like a normal blood cell. However, a few cell surface markers have been identified, including $CD34^+$. Although $CD34^+$ (the common indicator used for isolation) appears to be present on all HSCs, it is also present on many other cells, such as progenitor cells, so there is currently no available method to isolate a pure sample of HSCs directly from the body (Hematopoietic, 2005).

The use of HSCs through bone marrow transplants has been saving lives since its first success in 1969. Bone marrow has been traditionally taken from the donor's hip, but this is a relatively involved procedure, so now scientists obtain them from umbilical cord blood or from the peripheral blood. A compatible donor can now donate HSCs using peripheral blood, a much easier process to go through (Bordignon, 2006). Other sources still being researched include umbilical cord blood and fetal blood.

HSCs plasticity has also been taken advantage of; they have not only been used in the treatment of blood related diseases, but for cardiac damage as well. Clinical trials were performed that injected bone marrow stem cells into the hearts of heart attack patients who had suffered the attack approximately six years prior. The improvement in the patients who received the bone marrow rather than the placebo was less than 5%, but if the bone marrow used could be purified further to include a greater number of HSCs, a more significant difference may be observed (Couzin, 2006).

Neuronal and Cardiac Stem Cells

It was originally thought that neither the brain nor the heart contained adult stem cells, and that no regeneration of neuronal or cardiac tissue occurred after birth. However, this "fact" has now been proven incorrect. Neuronal stem cells (NSCs) were the first of the two to be found as early as 1993, located in two different regions of the brain, the subventricular zone and the subgranular zone (Morshead et al., 1993; Bjorklund and Lindvall, 2000). Several experiments in the 1990's proved the existence of NSCs, and in 2001 Rodney Rietze and his colleagues were able to characterize the NSCs found in the subventricular zone (Rietze et al., 2001). Previously, NSC's were identified according to their behavior *in vitro*, Rietze's research team used cell sorting techniques, sorting by size, cell surface markers and the binding of peanut agglutinin and the levels of heat-stable antigen (both used to determine presence of other adult stem cells), to identify NSCs (**Figure-4**). They determined that

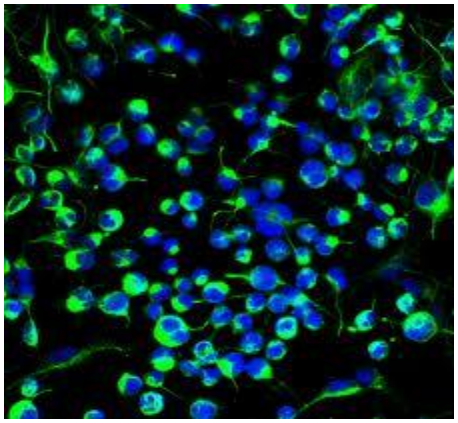

Figure 4: Photograph of Neuronal Stem Cells by Fluorescence Microscopy. The nuclei are stained blue. (Schaffer, 2011)

the NSCs isolated had a diameter greater than 12μm, minimal levels of both peanut agglutinin binding and of heat-stable antigen, and expressed the cell surface marker nestin (Rietze et al., 2001). Rietze and his colleagues also showed that the NSCs were capable of greater plasticity than originally thought. Not only could they develop into several types of neuronal cells, but also into other non-neuronal cells such as muscle cells (Cassidy and Frisen, 2001). The ability to culture and transplant NSCs into patients would be a tremendous step toward successfully treating patients with neurodegenerative diseases such as Parkinson's disease and Amyotrophic Lateral Sclerosis (ALS).

Shortly after the existence of neuronal stem cells was proven, two different research teams found evidence to support the existence of cardiac stem cells. The teams individually found cells that were able to restore damaged cardiac tissue *in vivo*. One team working at the New York Medical College found that lin^{-} $c\text{-}kit^{pos}$ cells located in the spaces between cardiac muscle cells were capable of self renewal and were also clonogenic (Beltrami et al., 2003). Another team led by Steven Bradfute and his colleagues found cardiac cells that expressed Sca-1 (stem cell antigen) had a high level of telomerase which is characteristic of stem cells (Oh et al., 2003). Even though these studies used mice and rats for their experimental models, the New York Medical College team also located cardiac stem cells in human cardiac tissue (Touchette, 2004). Hopefully, with continued research, these cardiac stem cells can be used to help treat those suffering from cardiac diseases.

Epithelial Stem Cells

It is well known that there is a high turnover of epithelial cells; something needs to replace dead skin cells and allow our hair to grow as it does. Through the use of different types

of labeling, researchers have identified a few types of epithelial stem cells. These cells include interfollicular stem cells, bulge stem cells, and sebaceous gland stem cells. These stem cells are responsible for the replacement of dead skin cells, the growth of hair, and the generation of oil producing cells, respectively (Blanpain, 2010). These are stem cells with specific tasks, and the stem cell markers that help identify them include β_1 integrin, cytokeratin-15, and cytokeratin-19 (Cotsarelis et al., 1999). In 2010, a research team led by Hugo Snippert found that epithelial cells that express Lgr6 (located in the isthmus which is a part of the hair follicle) were capable of producing any type of epithelial cell (Snippert et al., 2010). Scientists have already put epithelial stem cells to work through the use of skin grafts (Cotsarelis et al., 1999), and this new finding is an exciting advancement of our knowledge of these cells.

Mesenchymal Stem Cells

Mesenchymal stem cells (MSCs) are different from most other adult stem cells (with the exception of hematopoietic stem cells) because of their availability and current clinical use. Unlike many other types of stem cells, we know more about human MSCs than we do about animal MSCs. MSCs are found primarily in the bone marrow, attracted to plastic, and therefore relatively easy to extract from donors; however more recent experiments indicate MSCs are located in a variety of tissues (**Figure-5**). Flow cytometry is sometimes used to isolate MSCs but a reliable identifying combination of surface markers has not yet been found (Jackson et al., 2007).

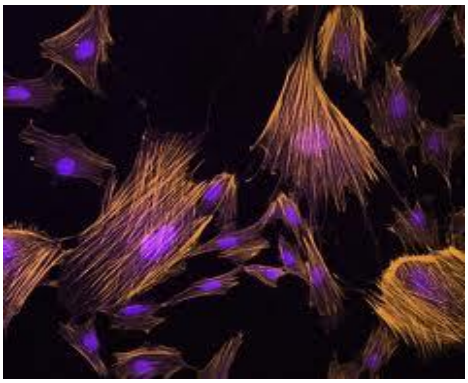

Figure 5: Fluorescent Photograph of Mesenchymal Stem Cells. Actin is stained purple. (Rosetti, 2011)

Once in culture, MSCs can be identified by their ability to form adipocytes, chondrocytes, and osteoblasts (types of mesenchymal cells). The plasticity of MSCs has been tested *in vitro* and *in vivo*, and the results have been astounding; MSCs appear to be able to form even muscle and neural cells (HemoGenix, 2009). MSCs have already been tested to determine their ability to repair damaged cardiac tissue in pigs, and their ability to repair cardiac tissue in heart attack patients is being studied (Goldthwaite, 2006). MSCs are favored for use in tissue repair because they lack expression of MHC II which decreases the risk of immune rejection (Jackson et al., 2007). These cells have the potential to be used in the treatment for many different types of diseases.

Chapter-1 Conclusion

The various types of stem cells discussed here all have different potentials for medical use. They do not all come from the same place, and therefore do not have equal ethical issues. Embryonic stem cells, induced pluripotent stem cells, parthenotes, and adult stem cells, all have different limitations and drawbacks; however, with continued research and proper legislation, many lives could be saved.

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Figure 3- Parthenogenesis. http://www.newscientist.com/article/dn3654-virgin-birth-method-promises-ethical-stem-cells.html

Figure 4: David Schaffer. University of California, Berkley. http://www.flickr.com/photos/cirm/3289060704/

Figure 5: Tony Rossetti. ASSR. http://www.asscr.org/index.php?id=1076

Chapter-2: Stem Cell Applications

One common misconception is that few lives have been saved by stem cell technology, and that such benefits to society remain far in the future. Both embryonic stem (ES) and adult stem cells (ASCs) are currently being used in research labs to further scientific progress and to lay the groundwork for eliminating specific diseases. Contrary to popular belief, some types of adult stem cells (specifically adult hematopoietic stem cells) have been used for decades to save thousands of lives for blood disorders. Other types of adult stem cells, and stem cells from fetal tissue, are already in use in human clinical trials. Human embryonic stem cells are still displaying potential in the laboratory, as scientists test their ability to form human tissues. The purpose of this chapter is to document stem cell benefits to society for four categories of disorders: blood diseases, diabetes, heart disease, and Parkinson's disease, to lay the groundwork for the next chapter on stem cell ethics.

Hematopoietic Stem Cell Applications

The use of hematopoietic stem cells (HSCs) has already been beneficial to society for decades. Bone marrow transplants (containing HSCs) were experimented with for years in the 1940's and 50's in patients, initially yielding unsuccessful results. Nobel laureate Thomas Donnall saw the need for more animal research, so he and his colleagues returned their focus to canines, the need for a more thorough eradication of the host marrow by using more intense irradiation, the need for a correct histocompatibility match, and the use of Methotrexate (better drugs have been found since then) for immunosuppression to decrease graft rejection. Altering these variables allowed Donnall and his team to solve technical problems and eventually move

forward with human clinical trials. In 1969, an infant was cured of an immunological deficiency using a sibling's bone marrow (Donnall, 1990).

Since the first one in 1969, bone marrow transplants have drastically increased in popularity. HSCs are traditionally isolated from bone marrow, but are now more easily obtained from cord blood or from peripheral blood. HSC transplants still carry the risk of graft versus host disease and host rejection, so finding a histo-compatible donor remains crucial. Histo-compatible donors (usually siblings) can help cure patients suffering from a vast range of diseases including leukemia, anemia's such as aplastic anemia and sickle cell, lymphomas, and inherited/inborn diseases such as Lesch Nyhan syndrome and osteoporosis (Hematopoietic, 2005).

In addition to treating blood disorders, HSC transplants have also been used in clinical trials for breast cancer (Rodenhuis et al., 2003; Tallman et al., 2003) and multiple myeloma patients (Child et al., 2003). For example, two studies performed to determine if high-dose chemotherapy along with an autologous HSC transplant could benefit women suffering from breast cancer were published in 2003. The study led by Sjoerd Rodenhuis and his colleagues included 885 women, ages 56 and younger. One group of 443 patients received a conventional chemotherapy treatment of five courses, while the other group of 442 patients received the same treatment with the exception of their fifth course, when they received the high-dose chemotherapy and the HSC transplant. They found that among the surviving patients, those receiving the experimental treatment had less aggressive tumors and a reduced incidence of relapse, although the overall survival rate did not appear to be affected (Rodenhuis et al., 2003).

Martin Tallman and his colleagues found similar results with their breast cancer patients. Their trial used 511 patients between the ages of 15 and 60, and the follow-up lasted for

approximately six years. The trial was set up very similarly to the Rodenhuis study. One set of patients received the conventional therapy, while the others received the high-dose chemotherapy and autologous HSC transplant. Again, the statistics showed that the overall survival was not affected by the experimental treatment, but rate of cancer recurrence was reduced (Tallman et al., 2003).

For multiple myeloma, the trial led by Anthony Child and his colleagues compared high-dose chemotherapy (melphalan) and autologous HSC transplants against using a conventional chemotherapy treatment. This phase III trial included 401 patients, 201 received the high-dose of melphalan and then 24 hours later received the HSC transplant, while the remaining 200 were treated conventionally. There were many complications for a large number of patients in both groups, both related and unrelated to the trial, but for those who received the high-dose therapy plus HSCs, an increase of one-year median-survival rate was observed. This encouraging outcome for multiple myeloma sets the stage for more trials (Child et al., 2003).

Thus, HSCs are well documented for treating blood disorders, and researchers are now showing that their use can be extended to other types of disorders including breast cancer and multiple myeloma. Also, HSCs appear to have the ability to form far more than blood cell components if conditions are right, so the plasticity of HSCs is being researched as mentioned in Chapter-1, and their ability to help in the treatment of other conditions such as cardiac damage will be discussed below.

Diabetes and Stem Cells

Diabetes is a disease that affects the body's production or response to insulin. There are two forms: Type-I diabetes is an autoimmune disease that destroys the pancreatic β-cells that

produce insulin, and in type II diabetes the body becomes insulin resistant. Insulin normally increases the cell's uptake of glucose, so the inability to produce or respond to insulin leads to an elevation of serum glucose, and its diminishment in the tissues. This disease affects millions of Americans (Goldwaithe, 2006), and researchers are hoping to find a cure using stem cells.

Animal trials have been used to determine the ability of stem cells to differentiate into insulin-producing cells. Qiao Zhou and his colleagues were able to reprogram adult pancreatic alpha cells *in vivo* to generate insulin-producing cells without using ES cells (Zhou et al., 2008). They found that a combination of three genes, Ngn3, Pdx1, and Mafa, when delivered using adenoviruses as vectors, reprogrammed adult pancreatic mature exocrine cells into β-cells (**Figure-1**). These induced cells had the same morphology as islet β-cells; however, the induced cells did not form islets and therefore may not be quite as effective (2008).

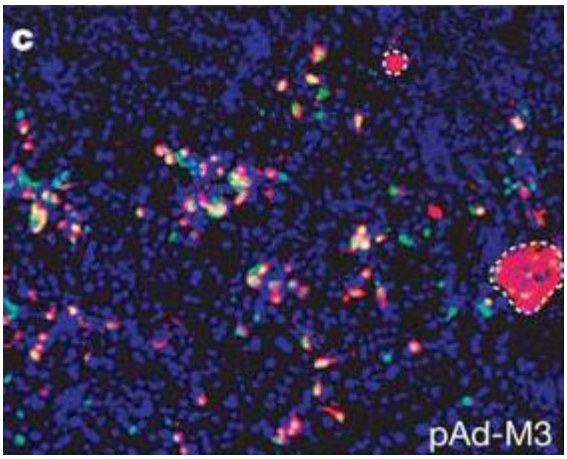

Figure-1: Reprogramming of Pancreatic Alpha Cells into Beta-Like Cells. Stained insulin^{+} cells (red) produced after infection with vectors carrying Ngn3, Pdx1 and Mafa (Zhou et al., 2008).

Another research team, led by Fabrizio Thorel and his colleagues, found another way to generate insulin-producing cells without the use of ES cells. Their research, using mice,

indicated that once the level of β-cells is negligible in the mouse, and there is a strong need of insulin, α-cells that would normally produce glucagon, can be reprogrammed to produce both glucagon and insulin. The amount of insulin produced varied, but some level of reprogramming was found in each tested mouse (Thorel et al., 2010). Both of these research teams have showed promising techniques for generating insulin-producing cells without using ES cells.

Researchers have successfully worked with human embryonic stem (hES) cells to create insulin-producing cells *in vitro*. The first two successes occurred in 2001 (Assady et al., 2001; Lumelsky et al., 2001). Suheir Assady and her colleagues allowed hES cells to spontaneously differentiate to form embryoid bodies from which they extracted cells at different time points to verify the presence of insulin. Insulin-producing cells were detected at approximately two weeks (Assady et al., 2001). Nadya Lumelsky and her colleagues were able to generate insulin-producing cells by isolating cells from embryoid bodies expressing nestin. These cells were then cultured on a medium that contained a basic fibroblast growth factor (bFGF). When the bFGF was removed, insulin-producing cells started to appear. However, these insulin-producing cells were more closely associated with neurons than pancreatic β-cells (Lumelsky et al., 2001). These two groups did not necessarily provide the most efficient way to produce insulin-producing cells, but they did provide a foundation to further the use of hES cells in research.

A more efficient process for differentiating hES cells was developed in 2006 by Kevin D'Amour and his colleagues who were able to efficiently generate insulin-producing cells *in vitro* that resembled immature fetal β-cells (D'Amour, 2006). Five main steps were taken to differentiate the hES cells to an insulin-producing state. First, it was important to ensure that the hES cells were able to come out of their state of self-renewal and prepare to differentiate. This

was done by reducing phosphoinositol-3 kinase signaling (PI-3 kinase signaling keeps the cell undifferentiated) and elevating the levels of activin-A (a growth factor) (D'Amour, 2006). Next, through the removal of activin-A, a primitive gut tube starts to be formed. Once the gut tube was formed, retinoic acid was added along with the hedgehog-signaling inhibitor KAAD-cyclopamine and growth factor FGF-10. This initiated the expression of Pdx1 (pancreatic transcription factor), so pancreatic organogenesis began. The retinoic acid was then removed and pancreatic epithelial progenitors and endocrine precursors were formed. This process takes about two weeks before the hES cells differentiated enough to start producing insulin and other pancreatic hormones such as glucagon and somatostatin. There is still much room for improvement, the amount of insulin-producing cells generated was approximately 7%, however, this is a step in the right direction, and the continued research gives hope for the thousands of people afflicted with diabetes (D'Amour, 2006).

Heart Disease and Stem Cells

Several different types of stem cells can potentially be used for the treatment of cardiac damage. hES cells are being investigated in labs, while different adult stem cells are already being used in clinical trials. The clinical trials documented thus far have had a mixture of results, but show promise for the future of adult stem cells as a treatment.

In 2001, Izhak Kehat and his colleagues were able to use hES cells to produce cardiomyocytes. They accomplished this by growing hES cells on a mouse embryonic fibroblast feeder layer, and as embryoid bodies formed (1884 total), contracting areas were found. These contracting areas (from 153 embryoid bodies) were then tested in several ways to determine their characteristics including staining, from which 29.4% of the contracting areas were found to be

cardiomyocytes (Kehat et al., 2001). This generation of cardiomyocytes has a lot of exciting potential, but an efficient method to produce them must be found.

Two small trials were conducted using different adult stem cells to determine if they could improve cardiac damage. Britten and his colleagues performed a clinical trial using both adult bone marrow and circulating blood progenitor cells. The 28 patients involved had suffered acute myocardial infarction (AMI), and were randomly given either one of the two progenitor cell types. Patients were tested four months after treatment for improvement. Through the use of magnetic resonance imaging (MRI), it was shown that the infarct size decreased (Britten et al., 2003). A phase I clinical trial was also performed using ten patients by Tomasz Siminiak and his colleagues. Skeletal myoblasts (**Figure-2**) were taken from the AMI patients, cultured, and were then transplanted at 3-4 weeks. A slight improvement was seen in the surviving patients (Siminiak et al., 2004). Larger clinical trials are needed to see if this is a viable treatment.

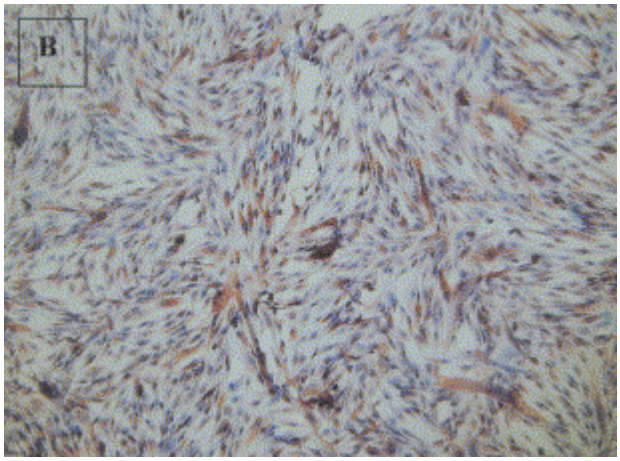

Figure-2: Stained Myoblasts Used for Transplant into Patients. (Siminiak et al., 2004)

Two slightly larger trials were conducted, but with conflicting results. A study conducted in Norway used fifty patients as a control, and fifty patients were given an intracoronary injection of bone marrow cells. The injections were given approximately one week after the AMI, and tests were performed up to six months later to determine improvements. The study was designed to detect an improvement of 5% or greater than the control group, but unfortunately that level of improvement was not detected (Lunde et al., 2006).

A double-blind trial conducted in hospitals in both Germany and Switzerland found more pleasing results. The control group received a placebo, and the experimental group received bone marrow cells that were enriched for HSCs. This trial (using approximately 100 patients between both control and test groups) also focused on the improvement of the left ventricle. A significant difference was detected in the experimental group, and although it was not specifically tested for, there was also a decreased recurrence of AMIs and decreases premature death (Schächinger et al., 2006). The results of this trial encourage the use of HSCs for the treatment of cardiac damage that affects millions of people world-wide (NIH Ch.6, 2006).

Parkinson's Disease and Stem Cells

Parkinson's disease is a devastating condition caused by the lack of dopamine release from dying neurons in the *substantia nigra*, causing a diminished control of motor function. Stem cell research has been promising in this area. Several successful tests have been performed with animal models, and hES cells have been differentiated into dopamine-producing neurons. Research has also moved into exciting clinical trials with varying results using either fetal tissue or adult neural stem cells transplanted into the *putamen* and/or *substantia nigra* (NIH Ch.3,

2006). These trials seek a balance between how many cells must be transplanted, the best regions for receiving the transplant, and the most beneficial source of transplanted material.

A trial conducted in the 1990's by Freed and his colleagues transplanted fetal tissue in an attempt to alleviate the symptoms of advanced Parkinson's disease. This double blind trial used forty patients; twenty in the experimental group were given transplanted human embryonic mesencephalic tissue in the putamen, and twenty in the control group were given a sham surgery. The transplanted tissue contained dopaminergic neurons taken from aborted fetuses (with the proper consent), and the patients did not receive any immunosuppression. In order to determine the level of improvement, or lack thereof, the patients kept diaries of their physical condition, and they were clinically evaluated at four, eight, and twelve months post-surgery. The results showed that the level of transplant survival did not depend on the patient's age, however, those in the trial that were 60 or younger showed physical improvement, while the older patients (for the most part) did not seem to benefit. Although this trial showed some benefit for the younger patients, in some cases too much dopamine was produced by the transplants which caused adverse side effects (Freed et al., 2001).

Another trial led by Ivar Mendez and his colleagues used three patients suffering from Parkinson's disease. They also used donated fetal tissue, but they gave immune-suppressants. The patients underwent two surgeries about one month apart, and the grafts were placed in both the putamen and the substantia nigra. Only two of the three patients completed the thirteen month follow up due to the third patient suffering unrelated complications. The results showed an improvement in the experimental group, in PET scans at six and twelve month intervals (Mendez et al., 2002).

A very exciting phase I trial was led by Michael Levesque (Levesque et al., 2009; Ertelt, 2009), who used adult neural stem cells extracted from a patient with advanced Parkinson's disease. These neural cells were expanded for six months, and then differentiated into dopamine producing cells. Immuno-staining for dopamine producing cells (**Figure-3**) and dopamine levels were quantified. Tests were also performed to make sure there were no viruses or bacteria present in the transplanted cells (Levesque et al., 2009). The expansion of a patient's own NSCs is more ethically acceptable than using fetal tissue or embryonic stem cells, and host rejection is less of an issue. Approximately nine months after the initial biopsy of neural stem cells, transplantation into the putamen was performed, and the patient was observed for five years post-surgery. The patient showed significant improvements for three years, however after the third year a sharp decrease in his condition was observed (Levesque et al., 2009).

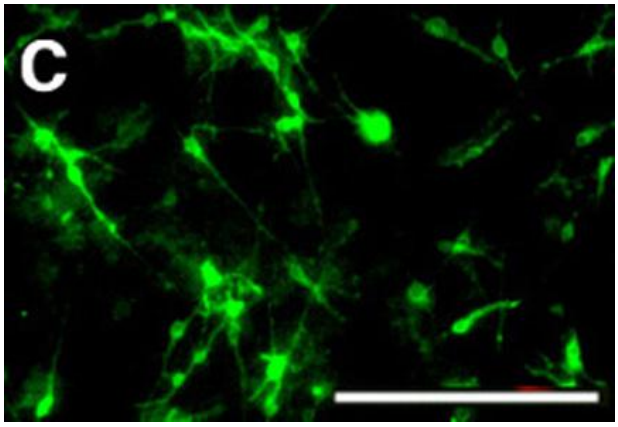

Figure-3: Fluorescent Image of Dopamine Producing Neurons Seven Days After Their Differentiation from Neural Stem Cells. The expansion of these cells allowed their use in transplants. (Levesque et al., 2009).

A phase II trial is being planned for this adult NSC approach that will involve 15 patients. At the moment the trial is on hold (Clinical, 2005), but hopefully its completion will result in lasting improvements for the patients involved, and it will bring us one step closer to permanently alleviating the suffering of those afflicted with Parkinson's disease.

Chapter-2 Conclusion

Stem cells have already been used to save thousands of lives from blood disorders, and there is a great deal of therapeutic potential for their use in other diseases. Their application could save millions of people suffering from a vast range of major diseases, from heart attacks to Parkinson's disease to diabetes. Although the use of embryonic and fetal stem cells is a highly debated topic, not all stem cells are controversial. Adult stem cells have been saving lives for years, and they have produced the most promising results in clinical trials. Although ASCs are harder to grow than ES cells, there are fewer ethical issues associated with the use of ASCs, and with the potential medical benefit these cells could provide, it is a research topic strongly worth supporting.

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Image References

Figure 1 – Zhou Q, Brown J, Kanarek A, Rajagopal J, Melton DA (2008) *In Vivo* Reprogramming of Adult Pancreatic Exocrine Cells to β-Cells. *Nature,* **455**: 627-632.

Figure 2 – Siminiak T, Kalawski R, Fiszer D, et al (2004) Autologous skeletal myoblast transplantation for the treatment of post-infarction myocardial injury: Phase I clinical study with 12 months of follow-up. *Am Heart J*. **148**: 531-537.

Figure 3 - Lévesque, Michel F., Toomas Neuman and Michael Rezak (2009) Therapeutic Microinjection of Autologous Adult Human Neural StemCells and Differentiated Neurons for Parkinson's Disease: Five-Year Post-Operative Outcome. *The Open Stem Cell Journal*, **1**: 20-29. http://www.neurogeneration.com/pdf/Levesque-MS.pdf.

Chapter–3: The Stem Cell Controversy

Introduction

The stem cell controversy is rooted in the differences in belief of when life truly begins. An individual's stance on when life begins directly affects their view on the use of a 5-day old embryo for research and the acceptability of using embryonic stem cells (ES) for research. For those that define life as beginning at conception, the destruction of a 5-day old blastocyst embryo to derive ES cells is immoral. However, those that believe that life begins at a certain point during pregnancy, for example, either after 40 days or after four months, support or tolerate the destruction of the embryo. For those that do not give the embryo the full status of a human being, but still deserving of some respect, a balance must be found of maintaining that respect (for example requiring their use to treat diseased people in need of a cure).

Most of the major world religions accept ES cell research on the grounds that the embryos come from a morally acceptable source and that the scientific motive is rooted in bettering humanity through healing. However, not all religions, most markedly Catholicism, have a tolerance for ES cell research. While some religions believe in the fetus obtaining a soul after a certain period of development, Catholics believes the zygote and pre-implantation embryo is a person and its destruction is infanticide. This difference in acceptance of the controversial research proves that the debate is rooted in the differences of view of the beginning of life in the womb.

Other than religious perspectives, there have also been opinions for and against this research using secular arguments, such as the "slippery slope" perspective (allowing human

therapeutic cloning will eventually lead to human reproductive cloning), and the principles of proportionality and subsidiarity. The law of proportionality can be used to defend ES research on the grounds that this resource is being used for a purpose worthy of its destruction. The principle of subsidiarity argues that research using alternative sources should be exhausted before ES cells are used, provided the alternatives can produce similar results (de Wert and Mummery, 2003). These perspectives exemplify the fact that this is not just a religious debate, and that this research sparks controversy among a much greater range of people.

The Five World Religions and Stem Cells

Catholicism

While some religions may have a divided opinion on the use of ES research, the Vatican, the official voice of the Roman Catholic community, has determined that all research involving the destruction of embryos is immoral. Roman Catholics believe that from the moment of conception, the zygote is a human-being and therefore given the full moral status and respect of an adult (Correa, 2000). The use of fetal tissue gained from induced abortions is also seen as unacceptable. The simplest way to explain a Catholic's view on this research is that the end never justifies the means. Catholics believe both induced abortion and the destruction of embryos are evil and unjustifiable. Therefore, neither action can be approved, even if it is in the name of potentially disease-curing research (Doerflinger, 1999).

Roman Catholicism also denies approval of the use of left-over embryos from IVF clinics. Their reasoning is that destruction is not necessarily the fate of the left-over embryos. It can also be said that the argument that researchers are using left-over embryos that would potentially be destroyed anyway is akin to the argument that euthanasia is morally acceptable

because the person will die soon anyway. The experimentation of fetal tissue obtained from induced abortions is also seen as immoral because this would be profiting from an intrinsically immoral action, and as stated, Catholics believe that the end never justifies the means (Pellegrino, 2000).

However, it is commonly mistaken that Roman Catholics disapprove of all stem cell research, and that is not true. One of the most common arguments against ES research is that there are good alternatives that have already shown promise. The Catholic Church is a strong advocate for adult stem cell research, and research using stem cells derived from umbilical cord blood (Smith, 2006). The support of this type of research has been emphasized by Pope Benedict XVI (Pope, 2008) and also by Pope John Paul II in 2005 (Pope, 2005).

Non-Catholic Christianity

Non-Catholic Christians seem to be slightly divided in their views of stem cell research. It can be agreed that adult and umbilical cord stem cell research is morally acceptable (United, 2004). However, the tolerance for ES research varies in this large complex group. Reverend John Fleischmann, a Lutheran minister, uses biblical passages to deem any use of ES research as unacceptable (Fleischmann, 2001). On the other hand, the United Methodist Church, while frowning upon the discarding and waste of any embryo, deems the use of embryos that would have otherwise been discarded from IVF clinics as acceptable, so long as the embryos were not produced in the name of research, and that these embryos are not used for profit (United, 2004).

Judaism

The Jewish community has a more liberal view towards ES research than one might expect, and this is due to two main reasons: their idea of the beginning of life, and the Jewish tradition of focusing strongly on one's duty to heal and take care of the ill. The Jewish perspective on the beginning of life varies. It can be safely said that they do not hold the same moral value for a fetus forty days or younger as they do for an older fetus or adult human being (Tendler, 2000). This accounts for the overall willingness of the Jewish community to accept ES research. For the first forty days after conception most Jewish people see the fetus as merely water, after that, the fetus gains greater moral significance. However, even an infant is not given full community membership status until thirty days after birth (Zoloth, 2000). Therefore, the destruction of an embryo that has not been implanted and has no hope of implantation certainly does not constitute murder according to Jewish law (Yearwood, 2006).

There are many Jewish texts that support this view (while there are still other passages that conservatives use against it). Some Rabbi's consider these embryos as *terefah* or *gavre ketila*, which is a person who is undoubtedly going to die, either from a terminal illness (the former term) or from being a criminal under a death sentence (the latter). These types of people are seen differently, and if the non-implanted embryo already determined to die is seen as a *terefah*, the goal of potentially life-saving research would justify its destruction (Zoloth, 2000).

These views allow for the majority of the Jewish people to take a lenient stance towards the ES debate. Along with their given value of the embryo, Jewish tradition focuses strongly on one's duty to heal and take care of the ill. For some, this duty even makes ES research mandatory, and the potential benefit to society justifies the destruction of the embryo (Dorff, 2000). However, while most claim that the use of grade III and IV blastocysts left to be

discarded from IVF clinics is morally acceptable, the creation of embryos for the express purpose of their destruction in the name of research is less morally justifiable, although for some it may be potentially acceptable (Zoloth, 2000). There has been no official decision on the exact opinion of the Jewish people for stem cell research. It is complicated because while most seem to agree that the destruction of an embryo is acceptable to attempt the curing of devastating diseases, some Rabbi's still give the non-implanted embryo more moral significance, while others argue according to the slippery slope argument (Eisenberg, 2006). So, while some in the Jewish community remain divided, it is safe to say that when it comes to the obtaining of embryos and fetal tissue from acceptable sources, ES research is not only acceptable, but a duty.

Islam

The Islamic community generally supports stem cell research, but there are a few conditions that must be met. The Islamic view on the beginning of life varies. Most would agree that even a zygote deserves to be respected; however, it does not gain the status of a full human being until after the fourth month of pregnancy where many Islamic scholars believe ensoulment occurs (Fadel, 2007). This belief of the beginning of life allows for Islamic approval of ES research.

However, the source of the embryos used for research is a crucial factor in their approval. It is widely agreed upon within the Islamic community that embryos cannot be made for the sole purpose of research. The accepted source of embryos are the embryos that would otherwise be discarded after IVF. This source is acceptable because Islamic law states that surrogate parenting is wrong, therefore the reproductive use of embryos developed from IVF can only be legally used for the parents whose egg and sperm were used (Siddiqi, 2002). The potential

benefit that can come from ES research, along with the fact that the excess embryos would be destroyed, makes the research using these excess embryos not only allowed, but an obligation (Weckerly, 2002).

While the Islamic community is generally in favor of ES research using the acceptable IVF reproductive sources, it is also stressed that scientific focus should be on adult stem cell research and what can be accomplished using less controversial sources of stem cells. Stem cells from adults and umbilical cord blood do not pose an ethical issue, and if these stem cells can be used to find cures, their use is preferable. It is also stressed that the use of extra embryos from IVF should not be used for profit, and measures should be taken to protect women from exploitation should the need for eggs increase (Siddiqi, 2002).

Buddhism/Hinduism

The beliefs of Buddhists are very different from those of the other four major world religions. They do not believe in "God" per se. They believe in rebirth and *karma*, the general idea of "what goes around comes around," and whatever one does in past lives affects their situation in this life (Manathera, 1994). Buddhism is also founded on a no-harm policy. These two fundamental views affect Buddhist's opinion on ES research. While there are no official rulings on Buddhist tolerance of this research, the general view of it is negative. Buddhists believe that from the moment of conception, that zygote is a person, therefore its destruction is immoral (Keown, 2004). While the morality of ES research is still uncertain, the research and use of adult stem cells does not pose an ethical issue for Buddhists (Holmes, 2004).

However, there are some ways that Buddhists could possibly justify the embryo's destruction (Promta, 2004). For example, when speaking at the Mind and Life conference in

2002, the Dalai Lama did not give approval or disapproval of ES research. His opinion seemed to be dependent on when the embryo/fetus gained a state of consciousness, and that would determine the acceptability of ES research (Dalai, 2002). Other considerations are whether the potential benefit to society justifies the sacrifice of embryos, and whether the embryo could be considered as a being willingly donating its life for a just cause (Promta. 2004). Until these answers are provided, it would seem that ES research is generally frowned upon by the Buddhist community.

Hinduism is very similar to Buddhism in that Hindu's believe in reincarnation and rebirth. Hindu's also believe that life begins at conception, and therefore ES research would be generally frowned upon (Teaching, 2006). However, there is no official Hindu ruling on the matter, and some accept ES researching using IVF's spare embryos (Walters, 2004). Those who accept ES research may believe that re-incarnation occurs later in pregnancy (Teaching, 2006).

Induced Pluripotent Stem Cells

The generation of induced pluripotent stem (iPS) cells in 2007 stimulated a lot of hope for an ethically sound replacement of the research being done on ES cells (Deem, 2009). While some argue that the reprogramming of a somatic cell to produce a pluripotent cell carries similar ethical issues as cloning through somatic cell nuclear transfer, many would argue that the ethical issues between the two are very different (Cohen and Brandhorst, 2008). The most important property of iPS cells that contribute to their position as a moral substitute for ES cells is that they do not come from an embryo, and therefore cannot be seen as taking a possible human life (Brind'Amour, 2009). Another positive feature of using iPS cells rather than ES cells is that women cannot be exploited by their use, as eggs do not need to be donated (Baylis, 2008).

These qualities provide two very convincing arguments for furthering the research of iPS cells and overcoming the involved complications of their use (as discussed in Chapter-1 regarding whether they are truly pluripotent and regarding their DNA mutation rate) rather than the complications of ES cells. Unless iPS cells can be super-manipulated to go beyond pluri-potency to attain full totipotency (and acquire the ability to form an adult if implanted), their use may be viewed as an ethical alternative to ES cells (Brind'Amour, 2009).

Chapter-3 Conclusion (Author's Opinion)

The stem cell research that has been accomplished to date, and research which has yet to be done, is fascinating. I fully support adult stem cell research, as I hope to one day be a part of it. However, I do have some reservations concerning their sources. I support furthering the research using adult stem cells and stem cells taken from umbilical cord blood and other pregnancy tissues, as an alternative to using ES cells. On the other hand, I cannot personally justify supporting ES research, nor can I personally justify the use of fetal tissue obtained from induced abortions. There are various reasons that led me to take this stance in the stem cell debate.

I was raised by a Roman Catholic family and attended Catholic schools from pre-school to high school, so I cannot deny the effect this has on my opinions. That being said, one of the goals I set for myself for this paper was to keep an open mind about ES research, and it is a topic that I have thoroughly contemplated. First of all, as with anyone else, my opinion of ES research is heavily affected by my view of when life begins. I argue that every embryo is unique, and while that group of cells is not a full person, it is the very beginning of human life with potential that should not be destroyed. This also includes the embryos taken from IVF clinics. This is an

opinion that I took a long time to form. I do feel that using an embryo for research, thereby allowing good to come of its destruction, is a better option than simply discarding it; however, I do not support IVF therapy as it produces too many embryos that end up being destroyed.

Secondly, ES research has not met with nearly as much success as adult stem cell research. The use of hematopoietic stem cells to treat various blood cancers is one of the best documented cases. And the research using adult stem cells from umbilical cord blood has resulted in successful clinical trials, as discussed in Chapter-2. I acknowledge that transplanted fetal tissue has been used successfully in a clinical trial to treat Parkinson's disease patients. However, a similar and successful clinical trial using a patient's own adult neural stems cells proved that there are less controversial alternatives that can be just as successful, if not more so. With respect to the point raised by some scientists that adult stem cells are generally harder to isolate and grow than ES cells in spite of the successes with HSCs and neural stem cells, I feel that this situation is improving almost daily with further research.

Lastly, another morally appealing alternative to replace ES cell research is the use of induced pluripotent stem cells. I strongly support the furthering of that research, and believe that it would be better to solve the complications that accompany the use of iPS cells as opposed to the complications that accompany ES cells. The great advantage of iPS cell research is that the material (i.e. skin fibroblast cells) is easily obtained compared to ES cells, and they do not pose the same ethical problems. This advantage has allowed the research of iPS cells to expand at an incredible rate over the past few years, as discussed in Chapter-1, and with the current fast paced progress, iPS cells hold great potential. And even if they eventually prove not to be truly pluripotent, they may prove potent enough to treat specific types of diseases.

The stem cell controversy has created strong feelings on both sides of the debate, each side with a legitimate argument. It does not just involve those who are religious, for this research has the ability to affect everyone. The potential benefits that could be brought to our society by the research using stem cells from all different sources is something that has the ability to impact this world, regardless of political and religious beliefs. One of the most important steps towards furthering all types of stem cell research is finding the correct balance of what research is ethically acceptable to pursue and what combination of efforts will produce the most beneficial results.

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Chapter 4 – Stem Cell Legalities

The type of legislation put in place both in the United States and internationally is rooted in culture. It is difficult for the United States to provide legislation for ES cell research that can be depended upon because the election of a new president can bring about a complete change in policy. This can be unnerving for scientists, as research takes years to perform and one research project can see several changes in the Oval Office. However, individual states can enact their own laws to supplement federal laws, and on a state level, there is usually a more consistent stance due to the individual culture within that state. This is also the case internationally. Many countries that share in a unified culture have a consistent long-term stance, and legislation that is reliable. The support of the federal government for ES cell research and the progress made in the field are directly related. When funding is not available, progress is slow and researchers are hesitant to engage their efforts in a project that would not receive support. This chapter will investigate the actions of varying US administrations, as well as the actions of US states and international governments and their effects on the overall progress of ES cell research.

US Administrations and Embryo Research

The Clinton Administration (1993-2001)

The origin of the stem cell controversy in the United States is rooted in the Clinton Administration. He was a very strong supporter of the earlier Roe vs. Wade (1972) decision to legalize elective abortions, and he was an important advocate for ES cell research to find cures for various devastating diseases (Clinton, 2004). Prior to Clinton's administration, the US government largely disapproved of both fetal tissue and embryonic research, which resulted in

bans and moratoriums placed on the availability of federal funding for research of that nature (Stem, 2009).

In 1995, two years after Clinton was first elected President, a National Institute of Health (NIH) panel made recommendations concerning which type of research should be given federal funding. Although President Clinton approved of their recommendation to support ES cell research, he did not approve of the creation of embryos solely for research purposes. In 1995, shortly after the NIH recommendations were made, Congress responded by passing the Dickey-Wicker amendment. This amendment forbade the allocation of any federal funding to research that destroyed embryos and/or created embryos solely for research purposes (Dunn, 2005).

However, the Clinton Administration found a slight loophole in the Dickey-Wicker amendment that could allow for the federal funding of ES cell research. Lawyer Harriet Rabb suggested that federal funding could be given to researchers working with ES cells as long as the cells were obtained from excess embryos from an IVF clinic provided by a privately funded organization. The resulting ES cells could be used for research backed by federal funds because the ES cells themselves do not comprise an embryo. Rabb's opinion provided the foundation for the NIH ES cell research guidelines of the Clinton Administration. These guidelines were strongly advocated for by President Clinton, however, in 2001 the Bush Administration reversed Clinton's work, and the 1999 NIH guidelines never resulted in federal funding for ES cell research (Dunn, 2005).

The Bush Administration (2001-2009)

Politicians have varying views on what research should be funded with tax payer money. Throughout the Bush administration, the Republican Party was divided on this topic. The

decision of President Bush to not use the NIH guidelines recommended during the Clinton administration was not shocking. As a presidential candidate, he clearly expressed his opposition to ES cell research (Stem, 2009). On August 9th 2001, President Bush declared federal funding would be available for research only using ES cell lines that had been derived prior to 9:00 PM that day (Holden and Vogel, 2002). Bush reasoned that these existing cell lines were derived from embryos whose fate had already been determined, and he would not support the further destruction of embryos with the backing of federal funding (Bush, 2006).

It was initially estimated that sixty ES cell lines would be available for federal funding under the guidelines set by President Bush, however, the number able to be distributed to researchers in the United States was much less. One year after President Bush put his guidelines into effect, only four eligible ES cell lines were actively being distributed. Although the number of eligible ES cell lines had grown since the initial projection, not all of them were useful; many were not robust enough for research purposes. Some of them had not been fully characterized and their credibility was questionable. Moreover, the laboratories that had derived the ES cell lines were reluctant to distribute to competing companies, and the price did not make it worth it. In addition, some arguing began over the commercial rights of the cells. Thus, the Bush restriction put on ES cell lines certainly took its toll on the progress of ES cell research (Holden and Vogel, 2002).

In 2006, President Bush used his right to veto for the first time, vetoing a bill the Senate passed which would have eased the 2001 restrictions. This vote was passed in the Senate by a 63-37 majority. Following the veto, the bill was debated in the House of Representatives, where a two-thirds majority vote was needed to overturn Bush's decision, but this vote fell short with a majority of 235 to 193. In addition to this bill, two other bills focused on stem cell research were

also being debated in congress. The "fetal farming" bill, which placed a ban on commercially producing human fetal tissue, was passed by both the House and Senate without opposition, and it was accepted by President Bush. However, a second bill, highly endorsed by President Bush that promoted stem cell research using alternative sources was not passed with the needed two-thirds majority (Bash and Walsh, 2006). This veto prompted action by both private investors and individual states to back the ES cell research that many believe is vital in the curing of devastating diseases (Holden, 2006).

The Obama Administration (2009-Present)

After almost eight years of having the Bush administration's restrictions of approximately 20 ES cell lines available for federal funding, President Obama within two months in office quickly reversed the limitations (Langer, 2009). NIH was then given 120 days to amend the federal funding guidelines from the Bush administration (Hayden, 2009). The goal of the new NIH guidelines was to provide more federal funding for ES cell research while maintaining strict ethical rules to ensure integrity of the funded work. One of the new guidelines called for a registry to be established that listed all of the eligible cell lines. The guidelines also mandated the use of embryos that would otherwise be discarded by the IVF clinics. Therefore, federal funding is not currently available for any ES cells that are derived from an embryo created solely for research. The guidelines also prohibit federal funding for somatic cell nuclear transfer (SCNT) and parthenogenesis, techniques that some researchers were hoping to obtain funding for (Holden, 2009). Also, the Dickey-Wicker amendment remains in effect; therefore federal funding still cannot be used directly for the destruction of embryos (Holden, 2008).

The final guidelines produced by NIH contain a few issues that many people feel still need to be addressed. One of the major issues is the lack of consent required from the gamete donors. The gamete donors currently sign a consent form that provides "blanket coverage" of what the IVF clinic can do with the embryos produced with the donor's gametes. The consent form is not detailed, and some believe that this should be changed. A proposed revision is to provide a consent form that allows the gamete donor to decide whether human ES cell research is an acceptable option for their spare embryos (Lo et al., 2010).

However, not all currently used ES cell lines were originally created following the new, more ethically strict guidelines. These older cell lines will be considered for funding on a case-by-case basis by a panel selected by NIH. Additionally, the cell lines accepted for federal funding during the Bush administration shall not be automatically grandfathered-in; their eligibility shall also be considered via case-by-case analysis by the selected NIH panel (Holden, 2009).

Another possible obstacle for some researchers, although inadvertent, is the restriction of ES cells derived from blastomeres, a process that does not destroy the embryo. This situation occurred when NIH defined ES cells as being derived from a blastocyst (a stage at which the embryo contains approximately 100 cells), which excludes cells taken from a blastomere (a stage at which the embryo contains eight cells) which would be grown to the blastocyst stage to produce the ES cell line. ES cells derived this way are being used in a clinical trial attempting to treat patients with Stargardt's disease. This trial had initially intended to use federal funding, but the revised definition created uncertainty about the research's eligibility. However, the research held so much promise that private funds were eventually found (Ledford, 2011). These new NIH

guidelines are not perfect, but they have assisted researchers hoping to use ES cells to provide treatments for a variety of diseases.

US State Laws

Following Bush's 2001 decision to ban federal funding to derive new ES cell lines, several states became proactive towards ES cell research (**Figure-1**, blue color). Three states will be discussed below that reacted by supplying state funding for grants and facilities. Although not discussed here, other states have enacted laws banning ES cell research and other states that have not taken action either way.

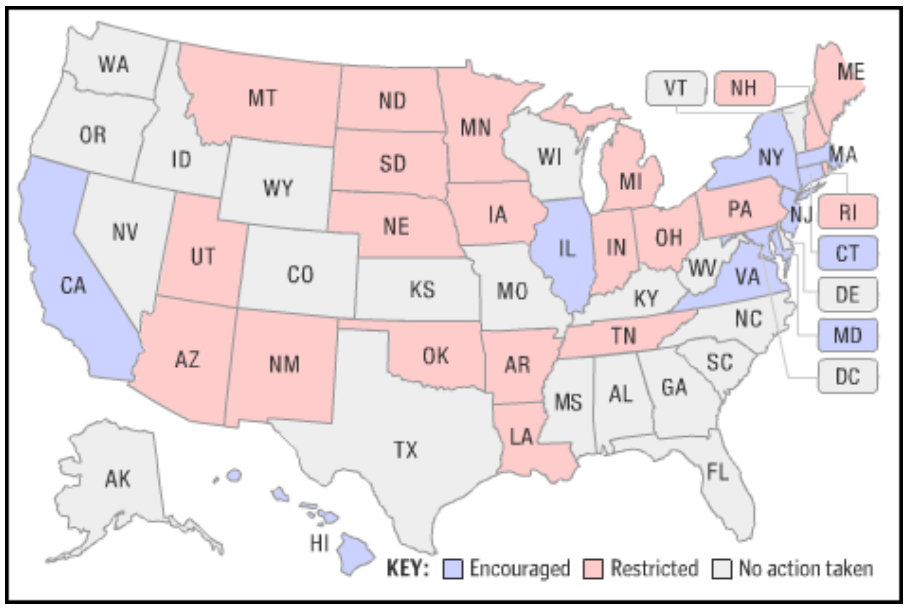

Figure-1: Stem Cell Actions Taken by Individual US States. Shown is a summary of the states who encouraged (blue), restricted (red), or provided no action (gray) for laws on stem cell research after President Bush's 2001 decision (Stem Cell, 2005).

New Jersey

In 2004, New Jersey became the first state to pass a bill enabling funding for stem cell research (Godoy and Palco, 2006). The state allocated $10 million towards stem cell research grants and research facilities. A large portion of it went towards New Jersey's institutions such as Rutgers University, and to private companies such as Reprogenetics LLC (The Commission, 2007). Although the state is primarily liberal and supports ES cell research, a ballot question in 2007 to allow the state to fund $450 million for ES cell research grants did not pass. Funding had already been procured for the building of a new facility in which this research could be performed, but additional funds were needed to support the research. But New Jersey had already accrued a lot of debt, and 450 million was a substantial amount of money to borrow that would possibly result in the increase of the already burdensome New Jersey property taxes. The proposal was therefore unpopular. However, there are plans to try to pass this ballot question again in the state's 2012 elections (Wadman, 2008).

California

California was the second state to respond to the 2001 Bush funding restrictions (Hayden, 2008). The state passed Proposition 71 in November 2004. This program provided $3 billion towards both ES cell research grants and the building of a new center, the California Institute for Regenerative Medicine (CIRM). This $3 billion was provided by the selling of bonds, and it was to be distributed through a ten year plan (Lao, 2004). Not only has the CIRM been given state funding, its initial establishment was due in large part to private donations, so there was much pressure for the CIRM to succeed (Hayden, 2008). However, there have been serious legal issues which have prevented the smooth allocation of most of the funds (Vestal, 2009). In the

meantime, California has been enthusiastically supporting the power of individual states to fund research that the majority of its citizens believe in.

Massachusetts

In the past ten years, Massachusetts has passed important legislation allowing funds for stem cell research. The state has moved forward with this initiative both with and without support from the governor. In 2005, then Governor Mitt Romney vetoed a bill that would have decreased some of the previous limitations placed on scientists working with ES cells. However, his decision was overturned by the state legislature and the limitations were reduced. The bill changed the authority responsible for approving ES cell research; before the bill was passed, ES cell researchers were required to obtain permission from the local district attorney before they could proceed, but with this state bill the requirement was replaced with regulations formed by the Massachusetts Health Department (Massachusetts, 2005).

The election of Governor Deval Patrick preceded the passing of a bill that included state funding for ES cell research, allowing Massachusetts to continue its position at the forefront of ES cell research (Marks, 2007). The bill that Governor Patrick supported was passed on June 16th, 2007 (News, 2008) and called for $1 billion of the state's money to be used for stem cell research and $250 million to be provided by matched funds. A large amount will be given towards the funding of research at public institutions, and it will also help fund the stem cell bank located in Worcester, MA as well as creating several "Life Science Innovation Centers." The passing of this bill ensured that work will be done for all aspects of stem cell research, from procuring the stem cells, to funding research with the cells, to making sure the state has the

resources to make the transition from experimental material to marketable product (Marks, 2007).

A large part of ES cell research in Massachusetts has been accomplished in the heart of the state, Worcester. Therefore, the allocation of funds provided by this bill will further Worcester's position as a center of Massachusetts stem cell research. The work performed in Worcester at the University of Massachusetts Medical School was rewarded with the procurement of approximately $8.2 million towards establishing the stem cell bank and registry as well as $12 million being given for research grants. There are many positive outcomes resulting from this funding, not only shall this funding help the continuation of important research, but it will also draw talented scientists to the area to increase the progress made (Shelton, 2007).

International Stem Cell Legislations

The stem cell regulations adopted by various international governments has everything to do with their unique culture and views of the beginning of life (as described in Chapter-3). The regulations vary from country to country (**Figure-2**), and brief examples of three different international approaches to the issue are discussed below.

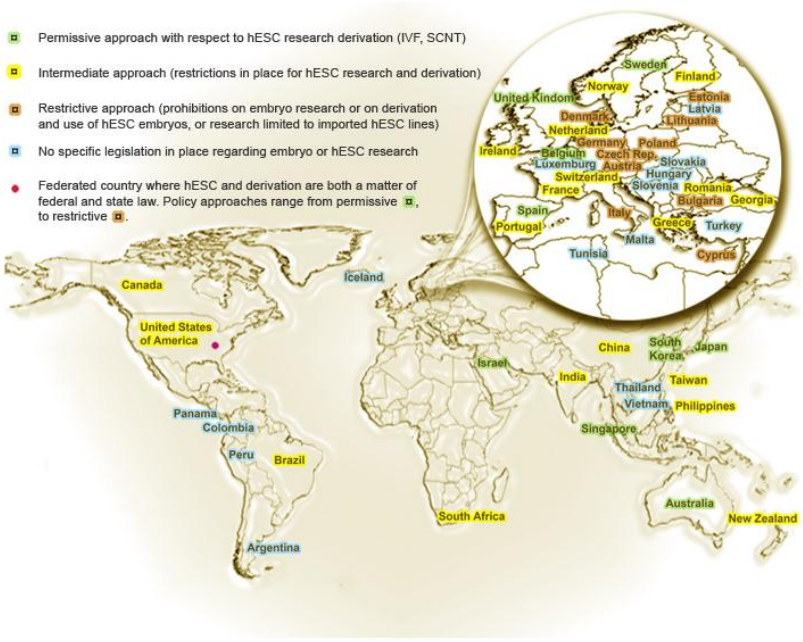

Figure-2: World Map Showing the Different Legislative Approaches Enacted for Embryo and ES Cell Research. Shown are countries with policies that are permissive (green), intermediate (yellow), restrictive (brown), non-existent (blue), or a combination of federal and state laws (red). (StemGen, 2008).

China

China has a very relaxed view on the ES cell debate. Confucianism is a widely held belief in China, and according to their culture, human life does not start until birth. ES cell research is widely supported, and the government provides ample funding for this research. Many Chinese researchers that have studied at American universities and worked in American laboratories go back to China because the government is more supportive of ES cell research than the US, and there is plenty of funding (Boyd et al., 2009). While China has been a strong supporter of ES cell research, some issues deter that country from becoming the dominant leader in this field. Fair patenting for intellectual property cannot be guaranteed due to their intricate and confusing

system. Also, research credibility is low, as a result of lax regulations on the peer review of published papers. However, if these issues can be sorted out by the government, China will most likely attract researchers from western countries and may eventually become the dominant leader in ES cell research (Barnes, 2006).

Germany

In comparison with China, Germany is an example of a country with a government stance that lies completely at the opposite end of the spectrum in the ES cell debate. Germany has very strict laws concerning ES cell research. Germany bans creating new ES cell lines, so the ES cell research done in Germany is performed using imported ES cells (Kim, 2002). The importation of these ES cells is strictly regulated. The only cells allowed to be imported are those that were harvested before 1 May 2007. While these regulations and restrictions are more stringent than those of other countries, this is a step forward in Germany's tolerance of the research. Prior to the parliamentary decisions concerning stem cell research in 2008, ES cell research performed by a German scientist internationally was considered a criminal offense. Although these improvements are a step in the right direction for supporters of ES cell research, it does not seem likely that Germany will heavily contribute to this new area of study (Herman et al., 2008).

Britain

Britain is an example of a country with an approach to the ES cell debate that seeks a compromise among the varying positions. The government decided that ES cell research was permissible, but strict regulations were to be put in place. The Human Fertilization and Embryology Authority (HFEA) was created to establish and enforce regulations. Another aspect

of Britain's control over ES cell research, unlike the United States, is that private companies do not have permission to do whatever research they please with their own funding; HFEA must approve all ES cell research performed in the country. The majority of Britain embraced the establishment of HFEA, but some believe that the council is severely lacking in representatives of the anti-ES cell research stance. However, this was widely accepted as a good compromise, and Britain's approach has been looked at as a model system (Boyd et al., 2009).

Chapter-4 Conclusions

Many different approaches towards ES cell research have been taken by US federal, US state, and international governments, to control the type of research allowed within each country. It is more difficult for the United States federal government to provide reliable legislation concerning ES cell research due to the election of various presidents that have drastically varying stances with an agenda for this research. However, the consistency of both state and international governments can be generally relied upon to provide basal support for the technology, and that is appealing to most researchers. Due to the high cost of this type of research, the stance that the federal US government takes towards stem cell research heavily affects the progress that can be made.

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PROJECT CONCLUSIONS

There are many different ways of looking at the ES cell debate, and many different aspects must be considered when deciding what types of stem cells and which techniques should be used. It is my opinion that ES cells should not be used for research. I believe that because the embryo, even in its earliest stages, contains the unique genetic material to create a human being, destroying that material and that potential for life is murder. There are many other avenues that can be used to advance stem cell research using adult stem cells in which no embryo is destroyed. For example, the trial performed by Michael Levesque using adult stem cells for treating Parkinson's disease, and the trials using adult stem cells from bone marrow to treat heart damage after acute myocardial infarctions as explained in Chapter-2, provide evidence that progress can made without the use of ES cells. The recent discovery of human iPS cells also provides hope that pluripotent cells can be obtained from adult skin cells without the use of an embryo, although their level of potency is not yet proven. Thus, I am not in favor of using excess IVF embryos, even when donor consent is provided. I cannot personally justify supporting IVF technology for infertile couples when so many embryos are left to be either discarded or destroyed in a laboratory. Nor do I favor creating embryos solely for research purposes, or the use of parthenote embryos.

I most closely identify with the legislation passed in Germany as discussed in Chapter-4, which only allows minimal ES cell research under strict conditions. While I agree with this legislation, I believe that a government should discourage all ES cell research and promote and give ample funding towards ASC and iPS cell research. There is so much potential for medical

treatments to alleviate numerous health conditions using these stem cells. In my opinion, as long as the experiments performed include humane treatment of test animals and the clinical trials are done in an ethical manner, than nothing else should hinder the progress of research using ASC and iPS cells.